

REMARKS

Claims 31, 33-38, 40, and 44-46 were pending.

Claim 31 has been amended to clarify that which Applicant regards as the invention. Specifically, claim 31 has been amended to recite "administering to an individual having a cancer". Claim 31 has been further amended to provide proper antecedent basis for claim 33, to recite "a *Quillaja saponaria* saponin or a chemically modified form thereof". Claims 33, 34, and 40 have been amended to correct grammatical errors and/or provide proper antecedent bases in view of the amendment to claim 31. New claims 47-50 have been added to correspond to the claim scope of the original claims 35 and 36, and claims 45 and 46 as dependent upon original claims 35 and 36, respectively. New claims 51-52 have been added to recite specific oligonucleotides comprising an unmethylated CpG dinucleotide. New claims 53 and 54 have been added to recite compositions comprising a mixture of substantially pure saponins. Support for these amendments can be found in the specification, for example, at page 7, lines 17-20, page 9, lines 17-19, page 21, line 20 to page 22, line 4, and page 24, line 15. No new matter has been added by these amendments. After entry of the present amendments, claims 31, 33-38, 40, and 44-54 will be pending.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

I. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 31, 33-38, 40, and 44-46 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for a method of treating cancer comprising administering to an individual in need thereof an effective amount of a composition comprising a *Quillaja saponaria* saponin, wherein said composition stimulates innate immunity, and said composition does not contain a vaccine antigen. The Examiner contends that the specification provides enablement only for a method of inhibiting tumor growth comprising administering to an individual an effective amount of a composition comprising *Quillaja saponaria* saponin to the vicinity of the tumor, wherein the composition stimulates innate immunity, and wherein said composition does not contain a vaccine antigen.

The legal standard for enablement was presented in Applicant's Amendment Under 37 C.F.R. § 1.114, filed on December 30, 2003.

In light of the legal standard, Applicant submits that the claims are enabled by

the instant specification. The instant application provides sufficient teaching to enable one of skill in the art to make and use the methods of the invention which involve administering a composition comprising a *Quillaja saponaria* saponin to treat cancer, without undue experimentation, as described below.

1. *Quillaja saponaria* saponins are effective in treating cancer

The Examiner contends that while the Declaration of Dr. Charlotte Kensil Under 37 C.F.R. § 1.132 filed on December 30, 2003 (“First Kensil Declaration”) provides *in vivo* data demonstrating that administration of QS21 intratumorally or in the vicinity of the tumor site inhibited tumor growth in a mouse model, it does not enable the invention to its full scope because it fails to demonstrate that the cancer is “treated”. The Examiner’s reasoning is that a method of “treating cancer … an individual in need thereof” encompasses both preventing and treating cancer. The Examiner concludes that any individual (who presumably does not already have cancer) does not want to have cancer and is “in need thereof”. The Examiner further states that the experiments described in the First Kensil Declaration demonstrate that tumor size stays the same upon intratumoral injection of QS21. Thus, the Examiner contends that this data suggests QS21 is only able to inhibit tumor growth.

The Examiner also contends that the standard of enablement is different from *In re Brana* because the present claims are drawn to a method of treating cancer, while chemical compounds were claimed in *In re Brana*. Therefore, the Examiner further contends that the specification needs to provide support for the prevention and treatment of cancer *in vivo*.

Without admitting to the propriety of the rejection and the Examiner’s construction of the claim, Applicant has amended claim 31 to recite a patient having a cancer. Thus, claim 31, as amended, no longer encompasses preventing cancer.

Moreover, Applicant respectfully submits that inhibiting tumor growth is a form of cancer treatment. Patients will greatly benefit if the tumor does not increase in size. This may prevent or delay a tumor from becoming metastatic or otherwise prevent or delay disease progression. In other words, a cancer therapeutic may reduce the rate of tumor growth when compared to a control in the absence of the cancer treatment. Thus, an effective cancer treatment does not have to reduce tumor size, if it can delay tumor growth and progression or maintain the tumor size.

Finally, with respect to the data presented in the First Kensil Declaration, Applicant points out that the *in vivo* tests in a mouse model are reasonably predictive of the

success of these compounds for treating cancer in humans. See *In re Brana*, 51 F.3d. 1560, 1567. The MPEP also addresses the relationship between an in vivo animal model assay and a claimed method of use stating that an in vivo animal model example constitutes a working example if the example correlates with a claimed method invention. See MPEP, Eighth Edition Rev. 2 (2004) § 2164.02. Applicant has previously demonstrated that the in vivo animal models used are art recognized models for a particular cancer. See Response Under 37 C.F.R. § 1.111 filed on October 20, 2004 at page 6.

Thus, Applicant respectfully submits that the evidence of record fully enables the claimed methods of treating cancer.

2. *Quillaja saponaria* saponins are also effective when administered away from the vicinity of a tumor

The Examiner seems to contend that administration away from the vicinity of a tumor is not enabled, i.e., that a *Quillaja saponaria* saponin is only able to inhibit tumor growth when administered in the vicinity of the tumor. Applicant respectfully disagrees.

The Declaration of Dr. Raphael Clynes provides experimental results demonstrating that QS-21 has antitumor activity when administered away from the vicinity of the tumor. The antitumor effects of QS-21 were evaluated in a B16F10 melanoma model/lung metastases mouse model. Subcutaneous injection of QS-21 was found to result in fewer tumor nodules in the lung. See Declaration of Dr. Raphael Clynes ¶¶ 7-8. This experiment demonstrates that administration of a substantially purified saponin, QS-21, in the absence of a vaccine antigen, can stimulate innate immunity so as to inhibit tumor growth distant from the site of administration of the saponin.

Thus, Applicant respectfully submits that *Quillaja saponaria* saponins are effective when administered away from the vicinity of a tumor.

3. *Quillaja saponaria* saponins share a common structure and function, which makes the use of modified or unmodified forms of *Quillaja saponaria* saponins to treat cancer predictable

The Examiner agrees that *Quillaja saponaria* saponins share a common structure that gives rise to the common innate immunity function, but does not agree that such common structure would be expected to function in the same manner with respect to increasing innate immunity and treating cancer. In particular, the Examiner contends that the Second Declaration of Dr. Charlotte Kensil Under 37 C.F.R. § 1.132 ("Second Kensil Declaration") and the cited references demonstrate that the common structure shared by *Quillaja saponaria* saponins regarding enhancement of adaptive immunity is in the context of

their use as adjuvants, not as cancer therapeutics. The Examiner further contends that the chemical modification of QS21 taught by Soltysik relates to its activity as an adjuvant. Applicant respectfully disagrees.

As discussed in the Second Kensil Declaration, *Quillaja saponaria* saponins share a common structure that gives rise to the common innate immunity function, and thus would be expected to function in the same manner with respect to increasing innate immunity and treating cancer. See Second Kensil Declaration at ¶ 4. *Quillaja saponaria* saponins QS-21 and QS-7 have been found to act similarly in innate immunity, for example, by enhancing natural killer cell lytic activity (see the specification, Figure 3 and page 35, lines 12-13). Enhanced natural killer cell lytic activity results in the induction of interferon gamma by the innate immune system. See Second Kensil Declaration at ¶ 8. Moreover, the ability of four structurally related *Quillaja saponaria* saponins, QS-7, QS-17, QS-18, and QS-21, to induce an IgG2a response is indicative of their ability to increase the innate immune response. See *id.* at ¶ 11. Thus, the Second Kensil Declaration demonstrates that the common structure of *Quillaja saponaria* saponins provides for a common ability to stimulate innate immunity.

The common structure of *Quillaja saponaria* saponins (as discussed in the Second Kensil Declaration §§ 4-7), including a triterpene backbone, a 2,3-glucuronic acid carboxyl group, and an acyl group, and the variations within such common structure among *Quillaja saponaria* saponins teach one of skill in the art what chemical modifications can be made to the *Quillaja saponaria* saponin structure without affecting innate immunity stimulating function afforded by these common structures. For example, based on the extremes in structure between QS-7 and QS-21, it is reasonably predicted that the length of the acyl chain and degree of glycosylation can be varied without loss of ability to stimulate innate immunity. See *id.* at ¶ 8. Moreover, as discussed below, modifications can also be made to the glucuronic acid carboxyl group, apparently without loss of such ability.

The Second Kensil Declaration also discussed the kinds of modifications that can be made to *Quillaja saponaria* saponins without adversely affecting their immunologic activity, including their ability to induce IgG2a. See *id.* at ¶ 12. The Second Kensil Declaration states that Soltysik teaches that derivatives of QS-21 containing a modification of a carboxyl group on glucuronic acid were able to induce IgG2a levels. As discussed above, the ability to induce an IgG2a response is indicative of an ability to increase the innate immune response. Thus, the chemical modification of QS-21 taught by Soltysik also relates to innate immunity.

The teachings of the Second Kensil Declaration demonstrate that *Quillaja*

saponaria saponins share a common structure that gives rise to a common ability to stimulate innate immunity, and shows the guidance available to the skilled artisan regarding which types of chemical modifications can be made that preserve such ability. The experiments presented in the First Kensil Declaration demonstrate that a *Quillaja saponaria* saponin in the absence of a vaccine antigen is effective in treating cancer. See First Kensil Declaration at §§ 5-7. There is an art-recognized connection between an enhanced innate immune response and treatment of cancer (see, e.g., the specification, at page 22, lines 16-17). In view of all of the foregoing, it would be predictable that *Quillaja saponaria* saponins, unmodified or chemically modified, would be effective in treating cancer.

Thus, Applicant respectfully submits that the specification, knowledge of one of skill in the art, the First Kensil Declaration, and the Second Kensil Declaration, demonstrate that one of skill in the art can readily follow the teachings of the specification to use a *Quillaja saponaria* saponin, unmodified or chemically modified, to stimulate innate immunity, and thereby treat cancer.

Accordingly, for the reasons presented above, Applicant asserts that the claimed methods are enabled. Thus, the rejection under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application. Withdrawal of the Examiner's rejections and early allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call the undersigned attorney at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

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Adriane M. Antler 32,605
(Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

Enclosures